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# Studies on Heterocyclic Enaminonitriles. V.[1] Reactions of 2-Amino-3-cyano-1-ethoxycarbonyl-4,5-dihydropyrroles with Acetylenic Esters

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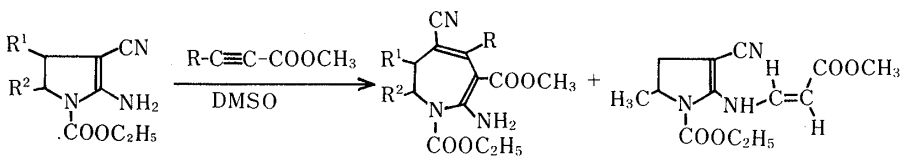
The reactions of 2-amino-3-cyano-1-ethoxycarbonyl-4,5-dihydropyrrole (Ia) and 2-amino-3-cyano-1-ethoxycarbonyl-5-methyl(or 4-phenyl)-4,5-dihydropyrrole (Ib or Ic) with dimethyl acetylenedicarboxylate and methyl propiolate gave the corresponding 7-amino-4-cyano-1-ethoxycarbonyl-2,3-dihydro-1*H*-azepines (IIa—c and IIIa—c). On heating with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, IIc and IIIc were converted into dimethyl 6-amino-3-cyano-5-ethoxycarbonylamino-4-phenyl-1,2-benzenedicarboxylate (V) and methyl 6-amino-3-cyano-5-ethoxycarbonylamino-4-phenylbenzenecarboxylate (VI), respectively.

**Keywords**——dimethyl acetylenedicarboxylate; methyl propiolate; 2-amino-3-cyano-1-ethoxycarbonyl-4,5-dihydropyrrole; 2,3-dihydro-1*H*-azepine; ring expansion; dehydrogenation; 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; ring contraction

Enamines react with activated acetylenes to give products derived from ring cleavage reactions of the initially formed cyclobutenes, which could be isolated in some cases.[2] The overall result with acyclic enamines is the insertion of a two carbon fragment into the enamines, and the reaction offers a method of ring expansion by two carbon atoms when cyclic enamines are used. We examined the reactions of 2-amino-3-cyano-1-ethoxycarbonyl-4,5-dihydropyrroles[3] (Ia—c) with acetylenic esters to see whether or not Ia—c behave as cyclic enamines (Chart 1).

When a mixture of 2-amino-3-cyano-1-ethoxycarbonyl-4,5-dihydropyrrole (Ia) and dimethyl acetylenedicarboxylate (DMAD) in dimethyl sulfoxide (DMSO) was stirred at room temperature, 7-amino-4-cyano-1-ethoxycarbonyl-2,3-dihydro-5,6-dimethoxycarbonyl-1*H*-azepine (IIa) was obtained in 61% yield (Table I).

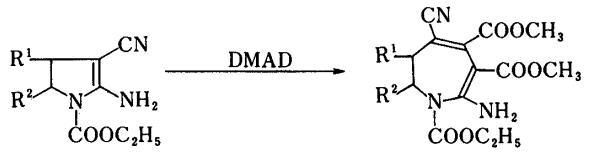
The results of elemental analysis and the mass spectrum (MS) ($M^+$ *m/z*: 323) indicated that IIa had been formed from one molecule of Ia and one molecule of DMAD. Its infrared (IR) spectrum exhibited bands due to a primary amino group at 3420 $cm^{-1}$ and 3280 $cm^{-1}$, a conjugated cyano group at 2200 $cm^{-1}$, and carbonyl groups at 1725 $cm^{-1}$ and 1680 $cm^{-1}$. The




II : R=$COOCH_3$ III : R=H
a : $R^1$=$R^2$=H, b : $R^1$=H, $R^2$=$CH_3$, c : $R^1$=$C_6H_5$, $R^2$=H

Chart 1

TABLE I. Reaction of Ia—c with DMAD



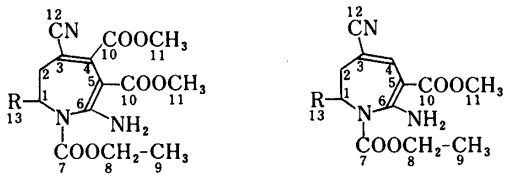

Ia—c IIa—c

a: $R^1=R^2=H$ b: $R^1=H$, $R^2=CH_3$ c: $R^1=C_6H_5$, $R^2=H$

| Compd. No. | Reaction conditions | | | | Yield of II (%) |
|---|---|---|---|---|---|
| | Molar ratio I:DMAD | Solvent | Time[a] (h) | Temp. (°C) | |
| Ia | 1:1.2 | DMSO | 4 | R.T | 61 |
| Ib | 1:1.2 | DMSO | 20 | R.T | 43 |
| Ic | 1:1.2 | DMSO | 24 | R.T | 54 |
| Ia | 1:1.5 | Xylene | 9 | Reflux | 30 |
| Ib | 1:1.5 | Xylene | 3 | Reflux | 16 |
| Ic | 1:1.5 | Xylene | 7 | Reflux | 42 |

*a*) The progress of the reaction was followed by thin layer chromatography. After all of Ia—c had been consumed, the reaction mixture was worked up.
R.T = room temperature.

TABLE II. $^{13}$C-NMR Chemical Shifts of IIa—b and IIIa—b
$\delta$ (ppm) from TMS in $CDCl_3$



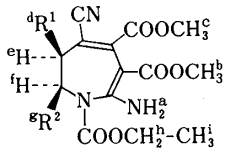

IIa—b IIIa—b

a: R=H b: $R=CH_3$

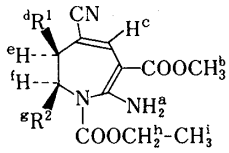
| Carbons | IIa | IIb | IIIa | IIIb |
|---|---|---|---|---|
| 1 | 52.0 (t) | 61.9 (d) | 46.1 (t) | 50.4 (d) |
| 2 | 31.4 (t) | 37.7 (t) | 32.1 (t) | 36.2 (t) |
| 3 | 110.5 (s) | 112.7 (s) | 98.8 (s) | 99.4 (s) |
| 4 | 153.3 (s)[a] | 153.0 (s)[b] | 132.2 (d) | 138.2 (d) |
| 5 | 89.3 (s) | 91.7 (s) | 87.9 (s) | 92.1 (s) |
| 6 | 157.9 (s)[a] | 155.1 (s)[b] | 160.9 (s) | 156.8 (s) |
| 7 | 145.2 (s) | 145.8 (s) | 153.1 (s) | 152.9 (s) |
| 8 | 63.2 (t) | 62.8 (t) | 63.5 (t) | 63.1 (t) |
| 9 | 14.4 (q) | 14.4 (q) | 14.3 (q) | 14.3 (q) |
| 10 | 166.2 (s)<br>167.9 (s) | 165.1 (s)<br>167.4 (s) | 169.4 (s) | 168.7 (s) |
| 11 | 51.6 (q)<br>52.6 (q) | 51.6 (q)<br>52.6 (q) | 51.7 (q) | 15.7 (q) |
| 12 | 118.1 (s) | 117.6 (s) | 122.3 (s) | 122.3 (s) |
| 13 | — | 21.3 (q) | — | 17.9 (q) |

Abbreviations: d, doublet; q, quartet; s, singlet; t, triplet.
*a*), *b*) These assignments may be reversed.

TABLE III. Spectral Data for IIa—c and IIIa—c




IIa—c




IIIa—c

a: $R^1=R^2=H$
b: $R^1=H$, $R^2=CH_3$
c: $R^1=C_6H_5$, $R^2=H$

| Compd. No. | IR $\nu_{max}^{KBr}$ cm$^{-1}$ | | | $^1$H-NMR spectra (ppm) in DMSO-$d_6$ solution ($J$ in Hz) | | | | | | | | | MS $m/z$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $NH_2$ | CN | CO | $H^{a,a)}$ | $H^b$ | $H^c$ | $H^d$ | $H^e$ | $H^f$ | $H^g$ | $H^h$ | $H^i$ | ($M^+$) |
| IIa | 3420<br>3280 | 2200 | 1725<br>1680 | 8.54<br>(br s) | 3.68<br>(s) | 3.54<br>(s) | 2.59<br>(t)<br>($J$=7) | | 3.92<br>(t) | | 4.08<br>(q)<br>($J$=7) | 1.15<br>(t)<br>($J$=7) | 323 |
| IIb | 3420<br>3310 | 2200 | 1720<br>1670 | 8.61<br>(br s) | 3.69<br>(s) | 3.56<br>(s) | 2.29—2.70<br>(m) | | 4.50—<br>4.91<br>(m) | 1.17<br>(d)<br>($J$=7) | 4.07<br>(q)<br>($J$=7) | 1.13<br>(t)<br>($J$=7) | 337 |
| IIc | 3400<br>3280 | 2200 | 1725<br>1680 | 8.69<br>(br s) | 3.68<br>(s) | 3.58<br>(s) | 7.20—<br>7.42<br>(m) | | 3.89—4.12<br>(m) | | 4.12<br>(q)<br>($J$=7) | 1.18<br>(t)<br>($J$=7) | 399 |
| IIIa | 3400<br>3240<br>3190 | 2180 | 1720<br>1655 | 8.78<br>(br s) | 3.68<br>(s) | 7.12<br>(t)<br>($J$=1.5) | 2.51<br>(t) | ($J$=6) | 3.59<br>(t) | | 4.13<br>(q)<br>($J$=7) | 1.20<br>(t)<br>($J$=7) | 265 |
| IIIb | 3360<br>3240<br>3200 | 2190 | 1715<br>1660 | 8.83<br>(br s) | 3.69<br>(s) | 7.11<br>(t)<br>($J$=1.5) | 2.40—2.60<br>(m) | | 4.38—<br>4.56<br>(m) | 1.14<br>(d)<br>($J$=7) | 4.11<br>(q)<br>($J$=7) | 1.15<br>(t)<br>($J$=7) | 279 |
| IIIc | 3380 | 2190 | 1720 | 8.89<br>(br s) | 3.72<br>(s) | 7.13—7.38<br>(m) | | | 3.63—4.17<br>(m) | | | 1.18<br>(t)<br>($J$=7) | 341 |

Abbreviations: br s, broad singlet; d, doublet; m, multiplet; q, quartet; s, singlet; t, triplet.
*a*) Disappeared on treatment with $D_2O$; amine ($-NH_2$) proton.

proton nuclear magnetic resonance ($^1$H-NMR) spectrum showed two three-proton singlets at $\delta$ 3.54 and $\delta$ 3.68 attributable to methoxycarbonyl groups and a broad two-proton singlet at $\delta$ 8.54 assignable to an amino group, in addition to the signals due to four protons of $C_2$–$C_3$ and five protons of an ethyl group. The $^{13}$C nuclear magnetic resonance ($^{13}$C-NMR) spectrum (Table II) showed signals due to four olefinic carbons. The $C_5$ olefinic carbon corresponding to the $\beta$-carbon of an enamine, like those of other enamines,[4] was shielded by the amino group at $C_6$. The structure of IIa was deduced on the basis of these data. In a similar manner, 2-amino-3-cyano-1-ethoxycarbonyl-5-methyl(or 4-phenyl)-4,5-dihydropyrrole (Ib or Ic) provided 7-amino-4-cyano-1-ethoxycarbonyl-2,3-dihydro-5,6-dimethoxycarbonyl-2-methyl(or 3-phenyl)-1*H*-azepine (IIb or IIc). The yields of IIa—c decreased when Ia—c and DMAD were refluxed in xylene. The spectral data for IIa—c are listed in Table III.

The reactions of Ia—c with methyl propiolate proceeded through the same orientation of addition as in the case of other enamines[2a,5] to furnish the corresponding 7-amino-4-cyano-1-ethoxycarbonyl-2,3-dihydro-6-methoxycarbonyl-1*H*-azepines (IIIa—c). However, the yields of IIIa—c were lower than those of IIa—c. Methyl propiolate seems to be less reactive than DMAD. In the case of Ib, methyl (*E*)-$\beta$-(3-cyano-1-ethoxycarbonyl-4,5-dihydro-5-methyl-2-pyrrolylamino)acrylate (IV) was formed as the main product (20%) accompanied with a small amount of IIIb (7%). The structures of IIIa—c were confirmed by the analytical (Table IV) and

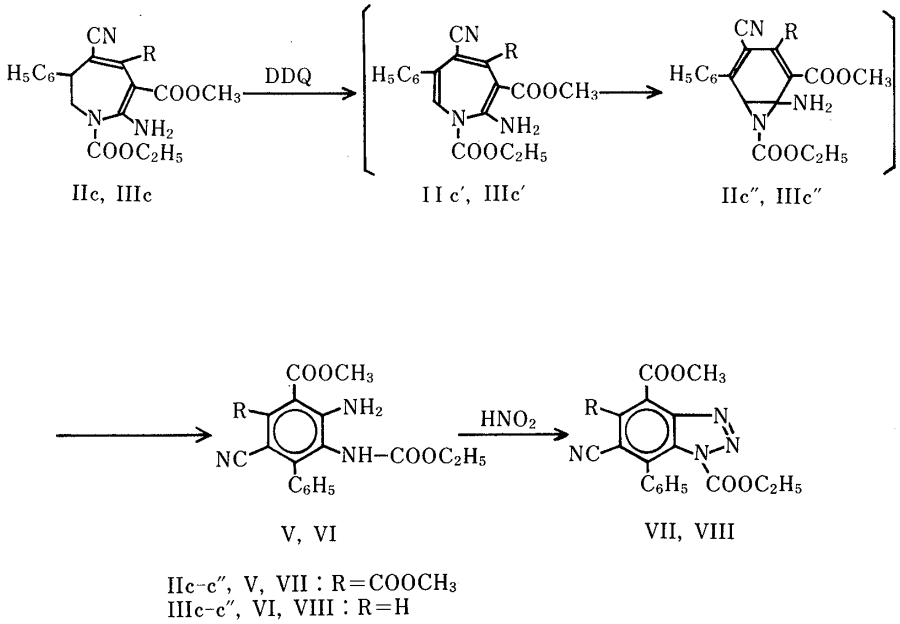



Chart 2

spectral data (Table III). In the $^{13}$C-NMR spectra of IIIa—b (Table II), the signals due to $C_5$ in IIIa—b appeared as singlets, whereas the signals due to $C_4$ appeared as doublets, indicating that the methoxycarbonyl groups are attached to $C_5$ in IIIa and IIIb. The IR spectrum of IV displayed a secondary amino band at 3280 cm$^{-1}$ and a cyano band at 2230 cm$^{-1}$. The $^1$H-NMR spectrum showed a broad one-proton singlet at $\delta$ 9.57 indicative of an amino proton, and a pair of one-proton doublets at $\delta$ 6.36 and $\delta$ 6.78 assignable to the $\alpha$ and $\beta$ protons of the methyl acrylate moiety. The *trans* configuration was assumed on the basis of the coupling constant ($J$=14 Hz).[6] Compound IV was therefore assigned as methyl (*E*)-$\beta$-(3-cyano-1-ethoxycarbonyl-4,5-dihydro-5-methyl-2-pyrrolylamino)acrylate.

Subsequently, we attempted to convert IIa—c and IIIa—c into the corresponding 1*H*-azepines by dehydrogenation. When a mixture of IIc and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in dioxane was refluxed for 11 h, dimethyl 6-amino-3-cyano-5-ethoxycarbonylamino-4-phenyl-1,2-benzenedicarboxylate (V) was obtained in 62% yield, none of the expected azepine (IIc') being isolated. Compound IIIc reacted with DDQ under the same conditions to form methyl 6-amino-3-cyano-5-ethoxycarbonylamino-4-phenyl-benzenecarboxylate (VI) in 48% yield. However, the reactions of IIa—b and IIIa—b with DDQ were unsuccessful. It is well known that *o*-phenylenediamines react with nitrous acid to give 1*H*-benzotriazoles.[7] For example, 1-ethoxycarbonyl-1*H*-benzotriazole is prepared by treatment of ethyl *N*-(2-aminophenyl)carbamate with nitrous acid.[8] On treatment with sodium nitrite in acetic acid, V (and VI) gave 6-cyano-1-ethoxycarbonyl-4,5-dimethoxycarbonyl (and 4-methoxycarbonyl)-7-phenyl-1*H*-benzotriazoles (VII and VIII). This finding suggests that the ethoxycarbonylamino group of V (or VI) occupies the position *ortho* to the amino group of V (or VI).

The formation of V (or VI) can be explained[9] by the scheme shown in Chart 2. The 2,3-dihydro-1*H*-azepines (IIc and IIIc) are dehydrogenated with DDQ to give the 1*H*-azepines (IIc' and IIIc'), which undergo valence isomerization to form the azanorcaradienes (IIc'' and IIIc''), and then the azanorcaradienes are converted to V and VI.

In conclusion, the present results suggest that Ia—c behave as cyclic enamines toward acetylenic esters.

TABLE IV. 7-Amino-4-cyano-1-ethoxycarbonyl-2,3-dihydro-5,6-dimethoxycarbonyl (and 6-Methoxycarbonyl)-1*H*-azepines (IIa—c and IIIa—c)

| Compd. No. | mp (°C) (Recrystn. solvent) | Appearance (Colorless) | Formula | Analysis (%) Calcd (Found) | | |
|---|---|---|---|---|---|---|
| | | | | C | H | N |
| IIa | 150—151 ($CH_2Cl_2$–petr. benzin) | Needles | $C_{14}H_{17}N_3O_6$ | 52.01 (51.88 | 5.30 5.41 | 13.00 12.82) |
| IIb | 166—168 ($CH_2Cl_2$–petr. benzin) | Needles | $C_{15}H_{19}N_3O_6$ | 53.40 (53.38 | 5.68 5.72 | 12.46 12.25) |
| IIc | 198—199 ($CH_2Cl_2$–petr. benzin) | Columns | $C_{20}H_{21}N_3O_6$ | 60.14 (60.05 | 5.30 5.29 | 10.52 10.16) |
| IIIa | 123 (Ether) | Prisms | $C_{12}H_{15}N_3O_4$ | 54.33 (54.10 | 5.70 5.73 | 15.84 15.83) |
| IIIb | 137 (Ether) | Columns | $C_{13}H_{17}N_3O_4$ | 55.90 (55.87 | 6.14 6.27 | 15.05 14.93) |
| IIIc | 159 ($CH_2Cl_2$–petr. benzin) | Prisms | $C_{18}H_{19}N_3O_4$ | 63.33 (63.19 | 5.61 5.61 | 12.31 12.16) |

## Experimental

DMSO was distilled under reduced pressure and stored over molecular sieve 4A. All melting points are uncorrected. IR spectra were recorded on a JASCO IRA-2 or a JASCO A-302 spectrometer. $^1$H-NMR spectra were taken on a Hitachi R-22 (90 MHz) or a JNM-MH-100 (100 MHz) spectrometer using tetramethylsilane as an internal standard. $^{13}$C-NMR spectra were obtained with a JEOL FX-100 (25.1 MHz) spectrometer using tetramethylsilane as an internal standard. Mass spectra were measured with a JEOL JMS-01SG spectrometer.

**Reactions of Ia—c with DMAD**——(i) A mixture of Ia, Ib or Ic (10 mmol) and DMAD (12 mmol) in DMSO (10 ml) was stirred for the indicated time (Table I) at room temperature. After the solvent had been removed under reduced pressure, the residue was purified by column chromatography on silica gel with $CHCl_3$ as the eluent to give IIa, IIb or IIc in the yields shown in Table I. The physical constants and analytical data of IIa—c are summarized in Table IV.

(ii) A mixture of Ia, Ib or Ic (10 mmol) and DMAD (15 mmol) in xylene (20 ml) was refluxed for the specified time (Table I). After work-up as noted in (i), IIa—c were obtained.

**Reaction of Ia with Methyl Propiolate**——A mixture of Ia (10 mmol) and methyl propiolate (12 mmol) in DMSO (10 ml) was stirred for 24 h at room temperature. The solvent was removed *in vacuo*, and the residue was purified by column chromatography on silica gel with $CHCl_3$ as the eluent to give IIIa (810 mg, 30%).

**Reaction of Ib with Methyl Propiolate**——A mixture of Ib (10 mmol) and methyl propiolate (12 mmol) in DMSO (10 ml) was stirred for 24 h at 80—85 °C. The solvent was removed *in vacuo*, and the residue was chromatographed on silica gel with ether–petr. ether (1 : 1) as the eluent. The first fraction gave unchanged IIb (10 mg), and the second fraction gave a mixture of IIIb and IV. Fractional crystallization from ether gave colorless prisms (560 mg, 20%) of the less soluble compound (IV), and colorless columns (190 mg, 7%) of the more soluble one (IIIb). Methyl (*E*)-*β*-(3-cyano-1-ethoxycarbonyl-4,5-dihydro-5-methyl-2-pyrrolylamino)acrylate (IV), mp 114 °C. *Anal.* Calcd for $C_{13}H_{17}N_3O_4$: C, 55.90; H, 6.14; N, 15.05. Found: C, 55.70; H, 6.22; N, 15.09. MS *m/z*: 279 ($M^+$). IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3280 (>NH), 2230 (CN), 1730 (>CO). $^1$H-NMR (in $CDCl_3$) $\delta$: 1.36 (3H, t, $J$=7 Hz, $-OCH_2-C\underline{H}_3$), 1.54 (3H, d, $J$=6.5 Hz, $C_5-C\underline{H}_3$), 2.31—2.43 (2H, m, $C_4$–H), 3.76 (3H, s, $-OC\underline{H}_3$), 4.25—4.41 (1H, m, $C_5$–H), 4.33 (2H, q, $J$=7 Hz, $-OC\underline{H}_2-CH_3$), 6.36 (1H, d, $J$=14 Hz, $-CH=C<^{COOCH_3}_{\underline{H}}$), 6.78 (1H, d, $J$=14 Hz, $\underline{H}>C=C<^{COOCH_3}_{H}$), 9.57 (1H, br s, >NH).

**Reaction of Ic with Methyl Propiolate**——A mixture of Ic (10 mmol) and methyl propiolate (12 mmol) in DMSO (10 ml) was heated at 80—85 °C for 24 h with stirring. The DMSO was removed *in vacuo*, and the residue was purified by column chromatography on silica gel with $CHCl_3$ as the eluent to give IIIc (1.51 g, 44%). Table IV shows the physical constants and analytical data of IIIa—c.

**Reactions of IIc and IIIc with DDQ**——A mixture of IIc or IIIc (2 mmol) and DDQ (680 mg, 3 mmol) in dioxane (20 ml) was refluxed for 11 h. The deposited crystals were removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ and the $CHCl_3$ layer was washed with 4% NaOH solution containing 1% $NaHSO_3$, and then water, dried over $Na_2SO_4$, and concentrated *in vacuo*.

(a) For IIc: The residue was recrystallized from $CHCl_3$–petr. benzin to yield dimethyl 6-amino-3-cyano-5-ethoxycarbonylamino-4-phenyl-1,2-benzenedicarboxylate (V) (490 mg, 62%) as colorless prisms, mp 190—192 °C. *Anal.* Calcd for $C_{20}H_{19}N_3O_6$: C, 60.45; H, 4.82; N, 10.58. Found: C, 60.60; H, 4.85; N, 10.57. MS *m/z*: 397 ($M^+$). IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3240, 3360, 3480 (–$NH_2$, >NH), 2200 (CN), 1700, 1740 (CO). $^1$H-NMR (in $CDCl_3$) $\delta$: 1.12 (3H, t, –$OCH_2$–$CH_3$), 3.89 (3H, s, –$OCH_3$), 3.98 (3H, s, –$OCH_3$), 4.03 (2H, q, –$OCH_2$–$CH_3$), 5.78 (1H, br s, –NH–CO–), 6.55 (2H, br s, –$NH_2$), 7.19—7.49 (5H, m, aromatic H).

(b) For IIIc: The residue was purified by column chromatography on silica gel with $CHCl_3$ as the eluent to give methyl 6-amino-3-cyano-5-ethoxycarbonylamino-4-phenylbenzenecarboxylate (VI) (325 mg, 48%), which was recrystallized from $CHCl_3$–petr. benzin to afford colorless columns, mp 131 °C. *Anal.* Calcd for $C_{18}H_{17}N_3O_4$: C, 63.71; H, 5.05; N, 12.38. Found: C, 63.75; H, 4.91; N, 12.53. MS *m/z*: 339 ($M^+$). IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3240, 3350, 3400 (–$NH_2$, >NH), 2200 (CN), 1680, 1720 (CO). $^1$H-NMR (in $CDCl_3$) $\delta$: 1.11 (3H, t, –$OCH_2$–$CH_3$), 3.91 (3H, s, –$OCH_3$), 4.03 (2H, q, –$OCH_2$–$CH_3$), 5.72 (1H, br s, –NH–CO–), 6.25 (2H, br s, –$NH_2$), 7.20—7.51 (5H, m, aromatic H), 8.23 (1H, s, $C_2$–H).

**Reactions of V and VI with Sodium Nitrite**——A solution of $NaNO_2$ (140 mg) in $H_2O$ (1 ml) was added dropwise to an ice-cooled mixture of V or VI (1 mmol) and conc. $H_2SO_4$ (1 ml) in AcOH (5 ml) with stirring, and the whole was stirred at room temperature for 2 h. The reaction mixture was poured into ice water, and the precipitate was collected, washed with ice water, dried, and recrystallized from $CHCl_3$–petr. benzin. The yields of VII and VIII were 84 and 89%, respectively.

(i) 6-Cyano-1-ethoxycarbonyl-4,5-dimethoxycarbonyl-7-phenyl-1*H*-benzotriazole (VII): Colorless needles, mp 128—129 °C. *Anal.* Calcd for $C_{20}H_{16}N_4O_6$: C, 58.82; H, 3.95; N, 13.72. Found: C, 58.89; H, 3.71; H, 13.81. MS *m/z*: 408 ($M^+$). IR $\nu_{max}^{KBr}$ $cm^{-1}$: 2200 (CN), 1730, 1770 (CO). $^1$H-NMR (in $CDCl_3$) $\delta$: 1.15 (3H, t, –$OCH_2$–$CH_3$), 4.05 (3H, s, –$OCH_3$), 4.07 (2H, q, –$OCH_2$–$CH_3$), 4.12 (3H, s, –$OCH_3$), 7.35—7.63 (5H, m, aromatic H).

(ii) 6-Cyano-1-ethoxycarbonyl-4-methoxycarbonyl-7-phenyl-1*H*-benzotriazole (VIII): Colorless plates, mp 143—145 °C. *Anal.* Calcd for $C_{18}H_{14}N_4O_4$: C, 61.71; H, 4.03; N, 16.00. Found: C, 61.90; H, 3.84; N, 16.08. MS *m/z*: 350 ($M^+$). IR $\nu_{max}^{KBr}$ $cm^{-1}$: 2210 (CN), 1725, 1780 (CO). $^1$H-NMR (in $CDCl_3$) $\delta$: 1.14 (3H, t, –$OCH_2$–$CH_3$), 4.05 (2H, q, –$OCH_2$–$CH_3$), 4.13 (3H, s, –$OCH_3$), 7.37—7.61 (5H, m, aromatic H), 8.45 (1H, s, $C_5$–H).

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